FOOD AND DRUG ADMINISTRATION

CENTER FOR BIOLOGICS EVALUATION AND RESEARCH

VACCINES AND RELATED BIOLOGICAL PRODUCTS
ADVISORY COMMITTEE

Open Session

Thursday,
August 7, 1997

Room 121, Building 29
National Institutes of Health
9000 Rockville Pike
Bethesda, Maryland

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C O N T E N T S

P R O C E E D I N G S (12:36 p.m.)

DR. FERRIERI: I'd like to open the session. I'm Pat Ferrieri, the chairperson of the Vaccines and Related Biological Products Advisory Committee. I would like to thank everyone, including our noisemaker, for joining us this morning. Just ignore it. We appreciate very much that the site visit took place, and our thanks to Dr. Griffin and Dr. Lemon and others who conducted the site visit for us.

I would like to start, if we could, by announcements from Mrs. Cherry.

MS. CHERRY: Yes, I have announcements. First of all, because this is a teleconference and it is being recorded, we will have a transcript from it, and we ask that you announce your name before you speak each time.

If you get cut off from this teleconference, the number to dial is 1-800-545-4387 to be reconnected. You should ask for Conference Number R38841.

DR. FERRIERI: Can you repeat that, please? I didn't have a pencil at the time.

MS. CHERRY: 1-800-545-4387.

DR. FERRIERI: 4387?

MS. CHERRY: 4387, and ask for R38841.

DR. FERRIERI: Three what 41? It's 38841, 38841?

MS. CHERRY: Yes, two eights.

Today, we'll have a short open session, and then we'll take a very short break to close the room for the committee deliberations after that.

Then I will read the meeting statement. This announcement is made a part of the record at this meeting of the Vaccines and Related Biological Products Advisory

Committee on August 7th, 1997. Pursuant to the authority granted under the committee charter, the director of the Center for Biologics Evaluation and Research has appointed the following individuals as temporary voting members: Drs. Diane Griffin and Stanley Lemon. I will add that, unfortunately, Dr. Lemon had a last-minute situation and could not be with us today.

Based on the agenda made available, it has been determined that all committee discussions at this meeting for the review of the intramural research program for the Laboratory of Method Development, Division of Product Quality Control, present no potential for a conflict of interest. In the event that the discussions involve specific products or firms not on the agenda, for which FDA's participants have a financial interest, the participants are aware of the need to exclude themselves from such involvement, and their exclusion will be noted for the public record.

With respect to all other meeting participants, we ask in the interest of fairness that they address any current or previous financial involvement with any firms whose products they wish to comment on.

With that, I will return the meeting to our chair.

DR. FERRIERI: Nancy, I think that you need to call the operator and see if she can cut off the people who are on hold who are not on line with us yet, because we will not be able to hear anything.

MS. CHERRY: Well, Denise has gone to do that.

DR. FERRIERI: Thank you.

Dr. Edwards, are you here yet? Dr. Adimora?

(No response.)

DR. FERRIERI: It appears that they are not.

We'll move ahead with the introduction to the program by Neil Goldman, who is associate director for research at CBER.

MS. CHERRY: The operator may come through, by

the way.

DR. FERRIERI: Thank you, Nancy.

Following him, we'll have Dr. Edward Fitzgerald, and Dr. David Asher following that.

I'd like to remind everyone to stay strictly on the schedule that Nancy has provided for us, so that we can

deal with our deliberations. If we don't have a quorum or if I have to drop out because we go overtime, then we'll have to start this all over again.

Dr. Goldman, are you there?

DR. GOLDMAN: I'm here.

DR. FERRIERI: Good morning.

DR. GOLDMAN: Good morning. How are you?

Well, I should say good afternoon to all, and I

also would like to thank you all for participating in this teleconference to review the results of the site visit for the Laboratory of Method Development. As you are aware already, the role of our product advisory committees is multifaceted and includes technical advice on biological products, classes, or groups of products; advice on appropriate design of clinical trials; advice on the use of surrogate markers --

MS. CHERRY: Can we stop here? Is that the operator trying to get through?

DR. FERRIERI: I don't know.

PARTICIPANT: It's virtually unhearable.

DR. FERRIERI: That's right. I mean, you might as well not be talking.

MS. CHERRY: I'm going to turn the volume up a little bit.

DR. FERRIERI: That won't help. Why do we have

a lull in the beeping right now?

MS. CHERRY: Well, maybe the operator was able to stop it. Maybe that's what that was.

DR. FERRIERI: It's stopped. If we could maybe resume, Dr. Goldman, and we'll test it.

DR. GOLDMAN: Sure.

If I may, as you're aware already, the role of our product advisory committees is multifaceted and it includes technical advice on biological products, classes, or groups of products; advice on appropriate design of clinical trials; advice on the use of surrogate markers for clinical endpoints; advice on interpretation of the results of clinical protocols; advice on risk assessment; and lastly, peer review of our intramural research programs and the research scientists who participate in them. While academicians usually are reviewed each time they submit and obtain a grant, our laboratories, which are funded intramurally, are reviewed every four years by a subgroup of you, our advisory committee. This mechanism is similar to the periodic lab review at NIH carried out by their

Boards of Scientific Counselors.

Historically, research has been an integral part of the mission of CBER, which is to protect and enhance the public health through regulation of biological and related products, including blood, vaccines, and

biological therapeutics according to statutory authority. The regulation of these products is founded on science and law to ensure their purity, potency, safety, efficacy, and availability. To fulfill this mission, we conduct research as an essential element of science-based decisionmaking on regulatory issues.

Uniquely among the other centers of FDA, we were mandated in 1955 by a PHS order that we "shall conduct research on problems related to vaccines, serums,

antitoxins, and analogous products, including blood and its derivatives." We "shall conduct other studies to assure safety, purity, and potency of biological products, to improve existing products, and to develop new products." This certainly would naturally extend to research to improve the techniques to assure the safety of existing products, as you will hear today.

As you already know, under the current administrative structure of CBER there are seven offices. Within each office, there are divisions composed of both laboratory-based and nonlaboratory-based scientists. Lab-based research is carried out in divisions within four offices: the Office of Vaccines, Office of Blood, Office of Therapeutics, and Office of Establishment Licensing and Product Surveillance. The Laboratory of Method Development, whose site visit you will be considering

today, resides in the Office of Establishment Licensing and Product Surveillance and within the Division of Product Quality Control.

We also have full-time regulatory scientists in application divisions within each of the four offices, which include clinical reviewers, pharmacologists and toxicologists, statisticians, and epidemiologists. Some of these staff -- for example, the statisticians and epidemiologists -- may carry out nonlab-based research.

In terms of logistics, the Center has about 400 lab-based scientists, of which there are approximately 85 who are principle investigators with permanent career appointments, and there are about another 85 who are what we refer to as conversion-track investigators, but may be more familiar to you as tenure track. These temporary employees, in this latter category, fall within our Service Fellowship Program, and they are commonly referred to as staff fellows.

In CBER, we have been operating under the researcher/reviewer model in which all researchers are fully integrated into the review process. Their regulatory

duties include review of INDs, PLAs, and BLAs; development and presentation of regulatory policy; meeting with manufacturers, sponsors, and advisory committees; and they also perform annual and prelicense inspections. The

percentage of time spent on regulatory responsibilities is usually commensurate with the length of time they have been with us and their employment status, and can vary from 10 to 50 percent.

The types of research which are considered mission-related include research on specific products that are under an active IND or license application; research on a specific policy issue related to a product or product class, disease area, or therapeutic modality to provide the foundation for evaluating future INDs and license

applications that will be submitted; and research associated with the development of methods and standards to which products can be compared. This latter category is very apropos to the research being carried out in the Laboratory of Method Development.

The request to you, the Vaccines and Related Biological Products Advisory Committee, as was originally related to the site visit team, chaired by Dr. Griffin -- with our thanks -- is to assess, considering both the strengths and weaknesses, the quality and appropriateness to the regulatory mission of the research being conducted, which includes the relevance, originality, creativity and level of sophistication, and also to evaluate the accomplishments of the individual scientist, which includes demonstration of independence, productivity, validity of

approaches, and research stature.

In addition, we have asked the site visit team, and thus through them this full advisory committee as well, to provide advice on the current scientific direction of a research program, whether new directions should be considered, any changes in the way a research program is administered or the level and utilization of resources, and lastly and very importantly, we asked for any advice on promotion or conversion -- that may be conversion to a senior investigator position, which is an independent investigator position, or staff scientist position, which is a dependent investigator position -- of some of our designated personnel. For example, we'd be interested in appropriateness of this action at this time.

Ultimately, the final report of the site visit team which is approved by this full advisory committee will be sent to the Center director, Dr. Zoon, who will pass it on to the appropriate office and division director, and finally down to the lab chief and the investigator who was reviewed. Any responses to comments in the final report will be prepared, and these responses will be forwarded back to this advisory committee.

Thus, this final report, which represents the peer review of our research programs and the scientists who participate in them, is a critical tool for us to use to

effectively manage the research programs in the Center as well as to aid us in making important personnel decisions. The need for a comprehensive in-depth evaluation is especially true in times of reduced resources when stringent research priorities must be set.

I now would like to turn this back to the chair, Dr. Ferrieri, who will be introducing Dr. Fitzgerald, the director of the Division of Product Quality Control, who will relay to you a more targeted view of the programmatic needs of his division and how the Laboratory of Method Development and their research programs fit into

the mission and address the needs of this division. I'd also like to thank the chair for the opportunity to speak to you today.

DR. FERRIERI: Thank you very much, Dr. Goldman, for such a succinct overview.

We'll proceed, then, with Dr. Fitzgerald. If there is any background noise you are hearing due to your own environment, I wonder if you could turn it down. I hear voices in the background. Maybe many of the others do as well. Either that or I'm having auditory hallucinations.

(Laughter.)

DR. FERRIERI: I hope it's not the case.

So the overview of the Division of Product

Quality Control will be presented by Dr. Edward Fitzgerald.

DR. FITZGERALD: Yes, good afternoon. Thank you very much. I would like to give a brief overview of the Division of Product Quality Control and then let Dr. David Asher discuss the Laboratory of Method Development more extensively.

The division consists of three laboratories -- the Laboratory of Standards and Testing, the Laboratory of Analytical Chemistry, and the Laboratory of Method Development -- and one administrative group, which is known as the Product Release Branch. This latter group has responsibility for the lot-by-lot release program for biological products.

At the site visit, we handed out a functional mission statement for DPQC. Unfortunately, that was not sent to you as a part of your package, so what I would like to do is to summarize the mission statement very briefly before turning this over to Dr. Asher.

First, our division performs quality control assays on biological products that are submitted for release action by the Center or for licensing actions. This testing occurs principally in the Laboratory of Standards and Testing and in the Laboratory of Analytical

Chemistry, but LMD is also now performing the MAPREC assay on a monovalent oral polio vaccine in parallel with the

monkey neurovirulence test. So this is then considered to be regulatory testing.

Second, we establish and provide the official U.S. reference and standard preparations that are used for the quality control tests performed by the manufacturers of these products, and also by our own laboratories here in the Center. This occurs in the Laboratory of Standards and Testing and we also have a clean room, a filling room, and a freeze drier, which we use to make these preparations.

Also, we coordinate the lot release program in the Center that I mentioned before in the Product Release Branch. As most of know, many of our biological products

are sent to CBER for review and testing before they are released for distribution by the manufacturer.

All three laboratories are pursuing an active applied research program that is focused on quality control testing, with our main goals being improvement of the test or development of a new test, with replacement of animals as our goal wherever possible. We have 21 active research projects in the division and the projects in the Laboratory of Method Development are among our most complex and our most highly visible.

Finally, as Dr. Goldman mentioned, all of our scientists participate in the regulatory review process for biological products, reviewing regulatory documents,

investigative new drug applications, and serving on the ad

hoc licensing committees.

Now, I would like to turn this over to Dr. David Asher, the chief for the Laboratory of Method Development, for a more extensive overview of that laboratory.

DR. FERRIERI: Thank you, Dr. Fitzgerald.

Dr. Asher?

DR. ASHER: Thank you, Dr. Ferrieri, Dr. Griffin.

Research in the Laboratory of Method Development is intended to improve regulatory testing of biologics, making tests more predictive, reliable, economical, and accessible, and to replace the use of animals, especially primates, whenever possible.

On February 21st, the laboratory presented for review six current projects. The professional staff under review included five investigators, three with permanent positions and one previously approved by the Center director for a permanent position when he becomes a citizen. The fifth investigator is now proposed for conversion to a tenured position. Each of the six projects is a cooperative effort led by one of those five people, but involving others. Three visiting professionals and

three highly skilled technical staff people also

participate.

The first three projects, each aimed at replacing the monkey neurovirulence test for safety and consistency of live oral poliovirus vaccine, began under the direction of Dr. lnessa Levenbook, retired chief of the laboratory. Two are collaborative studies in support of the World Health Organization's Campaign for the Global Eradication of Poliomyelitis. WHO's Global Program on Vaccines and Immunization identifies development of alternative models for investigation of attenuation and safety testing of OPV as a research priority. LMD serves as a WHO focal-point laboratory in those efforts.

The first project is MAPREC -- mutant analysis

by PCR and restriction enzyme cleavage -- a rapid and sensitive method for quantifying the small amounts of mutant nucleotides normally present in a viral quasispecies. Dr. Konstantin Chumakov's work confirmed the concept that there is a threshold for the content of potentially virulent mutants in OPV, and if the amount of mutant remains below that threshold, the vaccine is still fully attenuated. For regulatory purposes, he validated the ability of MAPREC to identify those lots of type 3 OPV that failed monkey tests. He has moved MAPREC from candidate WHO test for safety of type 3 OPV to what we anticipate will soon be accepted by WHO as a supplementary

or alternative test. During the past two years, Dr. Chumakov has guided all molecular biological aspects of the

WHO study, preparing candidate reference DNA and other standards needed to control the test and helping other participants to establish it in their own institutions.

In recent efforts to develop the test for type 2 OPV, Dr. Chumakov has determined a probable virulence threshold for content of mutant 481-G and he is investigating the possible contribution of two other mutants, 3363-G and 3364-A, to its virulence. A MAPREC for type 2 OPV may have to quantify mutant nucleotides at all three locations.

Establishing MAPREC for type l OPV has, paradoxically, been complicated by the fact that it is very stable, and no available lots of type 1 vaccine have convincingly failed monkey tests. However, tests of experimental preparations suggest that mutations 480-G plus 525-C, which are adjacent nucleotides across a stem loop in the 5-prime noncoding regions, are virulent, and no other suspicious mutants have been identified.

MAPREC has already been used by manufacturers as a screening test to reduce reliance on monkeys when establishing production, changing viral seeds, or altering conditions of production of OPV.

MAPREC should be applicable to regulatory

control of other live viral vaccines, vaccines for which, even if virulent mutations have not been identified, typical profiles of mutations that appear during production can be determined and monitored for consistency. We obtained outside funding for such studies, and anticipate beginning with mumps and yellow fever vaccines, to be followed by measles, rubella, and varicella vaccines, as well as several investigational live viral vaccines. We recently began a collaborative effort with the Argonne National Laboratory to develop a promising gel-microchip technology that we hope will detect mutants -- perhaps not as sensitively as MAPREC, and we plan to determine that -- in vaccines as well as adventitious agents.

Project 2, also initiated under Dr. Levenbook,

and led by Dr. Jeanette Ridge, is an attempt to develop a surrogate test in interferon-treated neuronal cell cultures predictive of the monkey neurovirulence of type 3 OPV. The study was based on the observation that yields of type 3 OPV propagated in SY5Y human neural cells were more inhibited by treatment of the cells with gamma interferon than were yields of a virulent vaccine revertant or wild-type virus. In repeated experiments, those differences, although variable in magnitude, were consistently observed and statistically significant. However, the assays are time-consuming, and their

predictive power for various lots of type 3 OPV and for other types of OPV remains undetermined.

Given that the two WHO-supported tests intended

to replace monkey testing are better developed and considering that global eradication of poliomyelitis is expected within three years, we have decided to complete only those additional experiments needed to describe the basic phenomenon -- measuring interferon-induced yield reductions for vaccines selected from Projects 1 and 3. As a new project, part of Project 6, Dr. Ridge has begun efforts to propagate and characterize a cell culture reported to support growth of some strains of the scrapie agent.

In Project 3, Dr. Eugenia Dragunsky has almost completed her projected goals for establishing a neurovirulence test for type 3 OPV in transgenic mice using the TgPVR21 line expressing the human poliovirus receptor gene, provided by our collaborator, Dr. Tatsuji Nomura, as a possible replacement for monkeys. Dr. Dragunsky perfected and instructed collaborating investigators in the delicate technique of intraspinal injection of mice needed to discriminate between attenuated and virulent preparations of type 3 OPV. The technique successfully identified all lots of vaccine failing the standard WHO monkey neurovirulence test, even so-called "marginal" lots

with only slightly elevated contents of the 472-C mutant, without rejecting any vaccine that passed the monkey test. Five other laboratories in the WHO study have now achieved a similar result with vaccines selected by Dr. Dragunsky.

Dr. Dragunsky has demonstrated promising results for type 2 OPV, successfully detecting several vaccine lots that failed monkey tests. One type 2 vaccine that several times passed monkey tests failed the mouse test, and possible contributions of mutants outside the 5-prime noncoding nontranslated region of the viral genome that I mentioned in Project 1 are under study now.

Production lots of type 1 OPV have, of course, not failed monkey tests, but nonetheless we have attempted to develop a mouse test for that type. At the time of the site visit, TgPVR21 mice had not successfully discriminated

experimental preparations of type 1 vaccine containing increased amounts of mutations at complementary nucleotides 480 and 525. However, recent experiments, using reduced infecting doses of virus, 10 to 100 TCID50, successfully discriminated a preparation containing 9 percent of those mutations from WHO type 1 reference vaccine containing 0.5 percent. We will attempt to improve the discriminatory ability of our test for type l OPV by increasing numbers of animals and selecting an optimal infecting dose of virus, as we did for type 3.

Project 4, Validation of Candidate Assays Intended to Replace the Monkey Neurovirulence Test of Live OPV and Development of Suitable Regulatory Tests, is one project that I initiated as a separate new project. It

seemed to me that each of the three previous projects shared common features and that each required similar methodological evaluation -- to optimize numbers of replicate samples in a test, to standardize viral infectivity titrations and other controls for the tests, and to specify validation criteria suitable for a regulatory assay and decision criteria for determining whether a test vaccine should be accepted or not. It seemed to me that such research should be a project in its own right, because its general statistical approach clearly applied not just to testing of OPV or other vaccines, but also to regulatory testing in general.

Since Rolf Taffs was doing a fine job in providing skilled, meticulous, and enthusiastic statistical support for Projects 1 and 3, he seemed to me to be an ideal person to lead this project. Dr. Taffs' analyses recently, in consultation with Drs. Henry Hsu and Peter Lachenbruch of our Division of Biostatistics and Epidemiology, have had practical importance guiding development of the decision models for both MAPREC and Tg mouse tests to be proposed to the WHO at a consultation of

the Global Program on Vaccines and Immunization next month.

Dr. Taffs will propose validation criteria for the mouse test based on historical mean rates of paralysis and mortality in groups of 30 gender-balanced mice injected with selected doses of reference vaccine and an innovative decision model based on the odds ratio for scores of clinical severity in mice injected with test vaccine compared with those injected with reference vaccine. He has also prepared other, more traditional, decision models as alternative possibilities.

Dr. Taffs has recently addressed relevant aspects of tests to evaluate removal of spongiform encephalopathy agents from production of FDA-regulated products.

THE OPERATOR: Hello. Ms. Nancy Cherry?

MS. CHERRY: Yes?

THE OPERATOR: I'm sorry. This is the operator. I have the party on the line who wants me to add them, Ms. Kathryn Edwards, who is not on the list.

MS. CHERRY: She should be on your list.

THE OPERATOR: I don't show her on the list. Would you like for me to --

MS. CHERRY: She is the next to the last name on your list.

THE OPERATOR: The next to the last name,

ma'am, I have Dr. Fernando Villalta.

MS. CHERRY: No, after that is Dr. Edwards, and then it's Dr. Diane Griffin.

THE OPERATOR: Okay. I don't have her.

MS. CHERRY: Well, anyway, we do want Dr.

Edwards with us, please.

THE OPERATOR: I do have Dr. Mary Estes, who it says do not call. Is she going to be joining this call?

MS. CHERRY: It was our understanding that she would not be joining this call.

THE OPERATOR: Do you want me to put Kathryn in her place, so I don't have to have one more line?

MS. CHERRY: Yes, please.

DR. FERRIERI: We're all here, but we --

PARTICIPANT: Are you still hearing that noise?

DR. FERRIERI: We're hearing the noise, but we lost Dr. Asher.

MS. CHERRY: No, he's here. He's here.

DR. FERRIERI: You're here?

DR. ASHER: I'm still here. I was waiting for arrangements for Dr. Edwards to be made.

DR. ADIMORA: But you had complained about background noise. Are you still hearing that, voices?

DR. FERRIERI: Occasionally, yes, Ada.

MS. CHERRY: We stopped when the operator broke

in.

DR. FERRIERI: Okay. Sorry, Nancy. I'm sorry for all these little personal bits that we've exchanged. We thought you were out.

MS. CHERRY: Okay. No, I guess the operator didn't have you plugged in when she was talking with us.

DR. FERRIERI: We can resume then, Dr. Asher. Sorry.

DR. ASHER: Thank you.

Dr. Taffs recently addressed relevant aspects of tests to evaluate removal of spongiform encephalopathy agents from production of FDA-regulated products, and he will be involved in developing statistically sound validation and decision criteria for them.

Project 5, Improved Potency Testing of Inactivated Poliovirus Vaccines by Protection of Transgenic Mice Against Challenge, is also led by Dr. Taffs. The WHO

recently failed to accept any international standard test for the potency of IPV. The tests currently used in the USA are not ideal. ELISA tests of D antigen do not always predict neutralizing antibody responses, and tests of immunogenicity for rhesus monkeys require a sensitive species and are expensive.

Dr. Taffs, aware of the shortcomings of existing tests, obtained some PVR21 mice from Dr. Nomura

for IPV testing. His preliminary results suggested that mice were protected by IPV against intraperitoneal challenge with wild-type 3 poliovirus and that the proportion of mice protected depended on the dose, schedule, and formulation of the IPV.

At the time of my arrival at LMD, it was clear

that IPV would soon replace at least the first two doses of OPV for immunizing most children in the USA, and that preparations of IPV combined with other vaccines would be developed. It seemed an appropriate time for LMD to develop improved IPV potency testing, and I encouraged Dr. Taffs to resume and complete the study with type 3 IPV and to use Tg mice for testing potency of type 1 and type 2 IPV. Those studies showed that transgenic mice could be used to assess potency of each of the three types, and that the mouse test appeared to be more predictive of antibody response than was D antigen content.

Furthermore, in addition to confirming that a second dose of IPV was needed for reliable immunization, with trivalent IPV, several other potentially important things were also observed. Monovalent IPV was more protective than trivalent IPV containing the same nominal human dose, and wild-type-derived IPV was more protective than Sabin attenuated virus-derived IPV.

Those findings suggest that immune response to

antigens in IPV may be affected by competition among types and that IPV prepared from attenuated virus may require a formulation different from that in current IPV to achieve the same response. Tg mice may provide a model suitable for examining immunogenicity of new formulations of IPV and of IPV in combined vaccines before clinical trials. The Tg mouse protection test may also be useful to compare with existing potency tests. We expect to participate in a collaborative study with investigators in the Division of Viral Products, who are attempting to improve D antigen ELISA tests, and from the Rijks Institute in the Netherlands, who developed an immunogenicity test for IPV in rats.

Parenthetically, I want to add here that, since February, Dr. Taffs, Miss Enterline, and I have been conducting a new study in collaboration with Dr. Richard Semba at Johns Hopkins and in support of WHO's Extended Program on Immunization addressing concerns that oral

iodine supplementation to the diets of children in EPI might interfere with their response to oral poliovirus vaccines. Results of the study should be completed within a month, and subject identifications will then be decoded.

Project 6, the last project, Transmissible Spongiform Encephalopathies: Assessing the Risk of Contaminated Products and Validating Methods to Reduce

Risk, is a project we began recently in response to recognition by FDA of two potential risks to human health posed by the agents of the transmissible spongiform encephalopathies. One, that Creutzfeldt-Jakob disease may be transmitted through biologicals and other materials of human origin, and two, that infectious agents causing TSEs of animals, like bovine spongiform encephalopathy and

similar diseases, may accidentally contaminate FDA-regulated products and transmit disease to humans. The committee was asked to review these plans because they represent a new area of research for CBER and for FDA.

Two projects have been approved and recently initiated, both attempting to develop assays validating methods purported to remove TSE agents from potentially contaminated materials. equipment, and work surfaces. The first assay was adapted from a standard test for bactericides, modified to use only disposable equipment. Rodent-adapted strains of scrapie agent dried onto glass in the presence of high organic load are exposed to disinfectants and sterilizing regimens. Residual infectious agent is then detected by disrupting the preparation and injecting material into rodents observed for a year or more for evidence of scrapie.

CBER's Animal Care and Use Committee approved the projects contingent on a demonstration that the assay

method itself was not unacceptably injurious to the animals, and that was successfully completed two weeks ago. Preliminary studies, already completed, suggest that none of the disinfectant methods currently in use was effective in removing all detectable infectivity.

We recently began a collaborative study with investigators in DPQC's Laboratory of Analytical Chemistry attempting to confirm reports that PC12 rat pheochromocytoma cells infected with the scrapie agent undergo marked reduction in GABA-related neurotransmitter activity while maintaining normal levels of adrenergic activity. Should that pilot study succeed, PC12 cells might provide a suitable simplified assay to detect scrapie agent as a preliminary screening test for disinfectant and sterilization methods. Methods that fail to remove infectivity of scrapie agent detectable in cell culture would clearly be inadequate for practical use, where infecting doses of agent are potentially much higher than those detected by cell cultures, and would not merit

further investigation in rodents.

Other proposed studies related to TSEs are summarized in your notebook. They can be conducted only in collaboration with investigators outside the FDA if and when additional funding becomes available.

That concludes my summary of research results

and goals of the Laboratory of Method Development, and I thank you.

DR. FERRIERI: Thank you, Dr. Asher.

We now need to clear the room, and Dr. Goldman and Mrs. Cherry will see that that takes place, so that the only ones who remain are those approved by Dr. Goldman.

(The open session was recessed, to reconvene after the closed session.)

DR. FERRIERI: I will now ask Mrs. Cherry if we have any speakers for the open public hearing.

MS. CHERRY: The answer is we have no one for the open public hearing, so I can return it to you for adjournment, after I say thank you to the committee.

DR. FERRIERI: I want to thank our committee, and also, again, the site team and Dr. Griffin. We will be seeing each other again as a team in October, I hope.

MS. CHERRY: We have October 15th and 16th reserved on the calendar. In about another week, week and a half, we will have our planning meeting, and I will know something more as to whether the meeting will take both days.

DR. FERRIERI: Well, I hope that all members of the committee will be there. I look forward to seeing all of you, and I would like to officially adjourn.

DR. GOLDMAN: And if I may, I'd like to also

extend my thanks and CBER's thanks to Dr. Griffin and her site visit team, which did an excellent job, and to the committee for getting together today.

DR. FERRIERI: Thank you, Dr. Goldman.

Goodbye, everyone.

(Whereupon, at 1:52 p.m., the open session was adjourned.)

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